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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,831	04/20/2004	Ronald M. Evans	SALK1520-3 (088802-8761)	5286

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/828,831	EVANS ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-6 are pending. Claims 1-6 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Information Disclosure Statement

The examiner acknowledges the statement in the cover letter of the IDS, indicating that all of the prior art has been previously submitted with the parent application 09/042488 (US-6,723,531) on the PTO-1449 and PTO-892 forms.

Some recent MPEP changes regarding the consideration of IDS may be of interest to the applicant.

Changes relevant to this application are in MPEP 609.02, A.2. "If resubmitting a listing of the information, applicant should submit a new listing that complies with the format requirements in 37 CFR 1.98(a)(1). Applicants are strongly discouraged from submitting a list that includes copies of PTO/SB/08 (PTO-1449) or PTO-892 forms from other applications. A completed PTO/SB/08 or PTO-1449 form from another application may already have initials of an examiner and the application number of another

application. This information will likely confuse the record. Furthermore, when the spaces provided on the form have initials of an examiner, there are no spaces available next to the documents listed for the examiner of the subsequent application to provide his or her initials, and the previously relevant initials may be erroneously construed as being applied for the current application."

Accordingly, none of the PTO-892 forms from the parent application will be considered for the instant application. However, despite the fact that the PTO-1449 forms are from the parent application, the examiner has reviewed and considered relevant the Information Disclosure Statements (IDS) filed on 15 November 2004 consisting of 8 sheets.

Priority

This application claims benefit as a Continuation of U.S. PAT 6,723,531, filed 16 March 1998 and is a Continuation In Part of U.S. Application 08/974,530 (Abandoned) filed 19 November 1997 which is a CIP of 08/628,830 5 April 1996 (Abandoned). The instant application has been granted the benefit date, 5 April 1996, from the application 08/628,830.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some 'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

Nature of the Invention

The invention as claimed, encompasses a method for modulating the expression of an exogenous gene *in vivo* (in a mammalian subject). The method requires successful expression of an exogenous of the modified ecdysone receptor and corresponding response element linked to an exogenous gene within the same cell in vivo.

The specification as filed discloses modified ecdysone receptor GEcR comprising: (a) a ligand binding domain that binds to an ecdysteroid, (b) a DNA-binding domain obtained from a DNA-binding protein, which binds to said response clement; and (c) an activation domain of a transcription factor, wherein at least one of said DNA-binding domain or said activation domain is not obtained from a native ecdysone receptor, with the proviso that when said activation domain is derived from a glucocorticoid receptor, said DNA-binding domain is not derived from a glucocorticoid receptor or a E. coli LexA protein; and (ii) a DNA construct comprising said exogenous gene under the control of said response element, wherein said response element: (a) is a modified response element which comprises, in any order, a first half-site and a second half-site separated by a spacer of 0-5 nucleotides; wherein said first half-site has the sequence:

--RGBNNM--, wherein each R is independently selected from A or G; each B is independently selected from G, C, or T; each N is independently selected from A, T, C, or G; and each M is independently selected from A or C; with the proviso that at least 4

nucleotides of each --RGBNNM--group of nucleotides are identical with the nucleotides at comparable positions of the sequence --AGGTCA--; and wherein said second half-site is obtained from a glucocorticoid receptor subfamily response element, (b) binds to said modified ecdysone receptor, and (c) does not bind to farnesoid X receptor (FXR).

While the Specification and issued U.S. patent 6,723,531 make clear that the previously described modified ecdysone receptor system is enabled for in vitro systems, the specification is not enabled for a method for modulating the expression of an exogeneous gene *in vivo* (in a mammalian subject).

Furthermore, the scope of instant application encompass the method as claimed wherein the exogenous gene is a therapeutic gene (e.g.: genes that encode human factors VIII and IX; genes that encode hormones such as insulin, parathyroid hormone, luteinizing hormone releasing factor (LHRH), alpha and beta seminal inhibins, and human growth hormone; genes that encode proteins such as enzymes, the absence of which leads to the occurrence of an abnormal state; genes encoding cytokines or lymphokines such as interferons, granulocytic macrophage colony stimulating factor (GM-CSF), colony stimulating factor-1 (CSF-1), tumor necrosis factor (TNF), and erythropoietin (EPO); genes encoding inhibitor substances such as α1-antitrypsin; genes encoding substances that function as drugs, e.g., genes encoding the diphtheria and cholera toxins; Specification, page 11, lines 7-20).

It is clear that the ultimate use of the claimed invention is for therapeutic control of exogenous genes through a regulated gene therapy system.

Working Examples and Guidance Provided

The specification successfully demonstrates regulation of exogenous gene expression controlled by the modified ecdysone receptor system in cell culture experiments. Furthermore, the specification teaches induction of exogenous gene expression in a transgenic mouse that has both of the following incorporated into its genome: (1) constitutively expressed modified ecdysone receptor and (2) an inducible reporter gene. Both of these examples show promise for the future of the invention. However, neither sufficiently demonstrates the clear goal of the invention as a transduced regulatable gene therapy system.

State of the Art and Analysis of the Issues

The modified ecdysone receptor system described in the specification and working examples of the instant application and in the claims of U.S. Patent 6,723,531, clearly limit the scope of enablement for the receptor system to that is described in the *Nature of Invention* section above. The state of the art, in U.S. Patent 6,723,531, and the working examples in the instant application limits the scope of the types of inducible expression systems to this modified ecdysone receptor system. There is insufficient guidance within the instant specification to enable an artisan to make and/or use a different system, based on other steroid receptors. The complexity of this system indicates that extensive experimentation would be required to develop an alternative system.

added. JF

In addition, there seem to be three clear problems to enabling a transducible form of the instant invention: (1) delivery of both the modified ecdysone receptor and the exogenous gene linked to the DNA binding domain to the same cell in the mammalian subject, (2) induction of the exogenous gene after treatment of the mammalian subject with the ecdysteroid, and (3) complicated nature of inducing therapeutic levels of exogenous genes from a transduced gene therapy system.

Generally, gene therapy is considered a highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. For example, in original clinical trial to treat adenosine deaminase (ADA) deficiency, patients received a total of 11 infusions of genetically modified autologous T-lymphocytes along with polyethylene glycol (PEG)-ADA. After 7 years of therapy no definitive conclusion is drawn as to the contribution of gene therapy to the present state of health of patients (Touchette, page 7 col.3, para.1; Anderson page 29 col.1, para.6). Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of

current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3).

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vectors comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes (Verma et al, page 241, col.1, par.3; col.3, par.1). Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to

selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefore would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4).

The instant invention as claimed requires the delivery of the ecdysone responsive receptor complex into a mammalian subject via viral and non-viral methods, wherein the expression of a therapeutic gene is modulated by the administration of a formulation carrying an ecydsteroid and an activator for the silent partner of the receptor complex. The claimed ecdysone inducible system comprises RXR and EcR which heterodimerize and transactivate the ecdysone response element capable of driving the expression of a gene of interest (specification Fig-2). It is not clear how both RXR and EcR constructs are delivered into a single cell in a mammalian subject. The specification fails to provide any guidance to selectively target both constructs into a single cell in order to achieve ecdysteroid induced responsiveness in vivo. At best the specification teaches ecdysone responsiveness in a cell line (293) *in vitro* via transient transfection of a modified ecdysone receptor VgEcR, a heterodimer partner (RXR) and an ecdysone inducible reporter gene (example-3) which c
modified
modulation of the expression of an exogenous gene in a mamr
organism. Since, the presence of an ecdysone inducible syster
primary example of instant invention, it is not clear how one skill
the invention as claimed in treating a whole organism without undue experimentation. Where the invention is applied to a whole organism, the example is directed to a transgenic mouse, into which a modified ecdysone receptor VgEcR, a heterodimer

partner (RXR) and an ecdysone inducible reporter gene (example-5) have been integrated into its genome. This transgenic example has constitutive expression of the components need for induction of the expressed gene by the steroid. While the transgenic example provides an excellent proof of concept for the operation of the constituent parts of the inducible system, it would not be a useful example for gene therapy treatments of adult mammals that were not genetically modified.

Even if both necessary components (EcR and ecdysone inducible reporter gene) are transduced to the same cell within the mammalian subject, would there be (1) sufficient expression of the modified EcR and (2) sufficient concentration of the ecdysteroid within the target cell after systemic administration of the steroid to the mammal, so that induction of the ecdysone inducible reporter gene could be expressed? The transgenic animal example overcomes the problem of having both (1) and (2), above, in the same cell. However, the level of expression in a transduced expression system will be lower than most similar systems incorporated into the genome of the host. Would the dosages of ponasterone used in example 3 and shown in figure 5 or, similarly, from the muristerone dose-response curves in figure 3A be sufficient to induce detectible levels of RNA or reporter protein when utilizing a transduced system?

Furthermore, the scope of instant claims encompasses the method as claimed wherein the exogenous gene is a therapeutic gene that could be used to treat a large number of potential diseases. The therapeutic genes suggested by the instant application for use in treating disease include factor VIII; factor IX; insulin, parathyroid

hormone, luteinizing hormone releasing factor (LHRH), alpha and beta seminal inhibins; human growth hormone; interferons, granulocytic macrophage colony stimulating factor (GM-CSF), colony stimulating factor-1 (CSF-1), tumor necrosis factor (TNF), and erythropoietin (EPO); α1-antitrypsin; diphtheria and cholera toxins (Specification, page 11, lines 7-20). The prior art does not demonstrate successful gene therapy treatments for the large array of diseases that could be treated using the genes listed above. The fact that there are some "partially successful" gene therapy treatments, such as the highly specific examples involving intratumoral injections of adenoviral p53 vectors, does not translate into wholesale application of the large number of claimed therapeutic genes claimed in the specification regulated through the inducible modified ecdysone system.

Considering the unpredictability in the state of gene therapy art the specification as filed fails to disclose a single working example wherein expression of a therapeutic gene is modulated by transducing an ecdysone inducible system into a mammalian subject. Thus, in view of lack of specific guidance in the specification and considering the state of undeveloped art, the skilled artisan at the time of filing would be unable to use the claimed invention, without an excessive and undue amount of experimentation. The experimentation required would include the delivery of both RXR and EcR constructs into a single cell in a mammalian subject and subsequent modulation of the transduced ecdysone inducible system using the formulation comprising a large number of naturally occurring ecdysones, ecdysone-analog and/or ecdysone mimics.

In conclusion, the quantity of experimentation required to make and use the invention, as claimed, is insufficient to enable the invention as a method of gene therapy that is used to transduce a variety of genes for treating numerous diseases.

Therefore it is unclear how one skill in the art would use the invention as claimed without excessive and undue amount of experimentation in view of the state of the art and the limited guidance provided in the specification.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave Nguyen** can be reached on **571-272-0731**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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